Cyclosporine A in the Treatment of Psoriasis: A Clinical and Mechanistic Perspective

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Cyclosporine A, a unique immunomodulatory agent, has been used increasingly over the last 5 years in the management of severe psoriasis. The remarkable efficacy of this drug coupled with its known immunosuppressive properties have enabled a further appreciation of the role of the immune system in the induction and maintenance of psoriatic plaques. Although acting primarily on T lymphocytes, there is also evidence for an effect of cyclosporine A on other constitutive cell types within the skin. The future use of systemically administered cyclosporine A in the treatment of psoriasis and other cutaneous diseases is dependent on the successful balance of efficacy and side-effect profile; namely, the dose-related problems of hypertension and nephrotoxicity. As a result of the toxicity encountered with systemically administered cyclosporine A, attempts to formulate a successful topical preparation for use in cutaneous disease are being made. The advent of cyclosporine A provides the dermatologist with a new therapeutic strategem in the management of psoriasis, although the long-term safety of such interventional therapy remains to be discerned. *J Invest Dermatol 95:53S–55S, 1990*

Cyclosporine A (CsA) is a lipophilic cyclic undecapeptide derived from the soil fungus *Tolypocladium inflatum gams*. Although initially developed as an antifungal agent, this property was found to be limited. Borel, in 1976, was the first to recognize the unique immunosuppressive properties of CsA [1], and by 1978 it was being used in the prevention of graft rejection following organ transplantation.

Since that time literature has burgeoned with case reports and studies of the use of CsA in a whole array of immune-associated diseases, of which psoriasis is but one of many. Indeed, the first report of the efficacy of CsA in the treatment of psoriasis was serendipitous: Mueller and Hermann [2] reported on the coincident improvement of psoriatic plaques in four subjects being treated with CsA for their arthritis. The dermatologic world took little heed of this 1979 report, and it was not until 1984 that interest was stimulated. This resulted in several uncontrolled short-term studies and one double blind placebo controlled study (Reviewed in [3,4]), which combined to show that CsA was indeed an effective drug in the treatment of psoriasis, whether it be erythrodermic, pustular, or chronic plaque. This short summary will attempt to define our current knowledge concerning the use of CsA in the management of severe psoriasis and what is known about the mechanism of action of CsA as it pertains to this disease.

CLINICAL USE

CsA is administered as a once daily oral dose calculated on a mg/kg basis. Approximately 40% of the oral dose is absorbed with a 25% hepatic first pass effect. Metabolism is almost entirely by the hepatic cytochrome P-450 III A system, and as a consequence concurrently administered drugs that can interfere with this enzyme system can significantly alter CsA blood levels [4]. For instance, drugs that inhibit or share the cytochrome P-450 system such as ketoconazole, erythromycin, danazol, corticosteroids, and calcium channel blockers can raise CsA blood levels. Cytochrome P-450 inducers, i.e., phenobarbitone, phenytoin, and rifamipicin, can lower CsA levels.

The therapeutic regimens of CsA used in the management of psoriasis are still in the experimental phase. In essence, because of dose-related side-effects, the lower the daily dose of CsA the safer it is. Indeed most studies have used low dose CsA, i.e., <6 mg/kg/d, with doses as low as 1 mg/kg/d being efficacious in some individuals. It seems that the majority of patients can be controlled on 3–4 mg/kg/d, and even with long-term treatment of up to 3 years the average daily dose is only 3 mg/kg [5]. At 3 mg/kg/d, clearance of severe psoriasis in a substantial number of patients can be expected by 6 weeks, and at 14 mg/kg by 2 weeks. Although blood CsA levels should be carefully monitored, they can be used only for side-effect elimination and frequently bear no direct relation to the therapeutic effect.

The hopes for CsA as a cure for psoriasis appear to be unfounded, as the majority of patients in all studies, to date, experience relapse of their disease on stopping CsA; however, rebound or flare beyond baseline severity has not been reliably documented.

Combination therapies may offer an alternative treatment route. Clobetasol propionate 0.05% ointment in combination with CsA 3 mg/kg/day for the first 2 weeks of CsA treatment brings about faster clearing of psoriasis than with CsA alone but does not significantly slow the relapse rate. It should be stated that the combination of CsA with PUVA or intensive UVB therapy is not to be recommended in view of the increased risk incurred by the use of an immunosuppressive drug with a potential skin carcinogen.

Psoriatic arthritis also responds well to oral short-term CsA treatment [4] at a dose of 6 mg/kg/d, although it seems that the dose required to control the arthritis is more than that required to control the skin lesions of psoriasis.

The serious, and probably limiting, side-effects of the use of CsA in the management of psoriasis are dose-related; namely, nephrotoxicity and hypertension.

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Abbreviation:
CsA: Cyclosporine A

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Nephrotoxicity can be either acute, manifested as a reversible rise in serum creatinine soon after the initiation of treatment, or chronic, characterized as renal interstitial fibrosis and tubular atrophy. Predisposing factors in chronic nephrotoxicity are old age, hypertension, and concurrent usage of other nephrotoxic drugs such as aminoglycosides and NSAID. The mechanism whereby CsA induces renal toxicity is not fully understood but in part resides in a direct effect on alteration of renal blood flow by inhibition of local prostaglandin production. The risk of nephrotoxicity can be lessened by using low doses of CsA, i.e., <5 mg/kg/d, by frequent monitoring of serum creatinine (serum creatinine should not be allowed to rise more than 30% above baseline), and by measurement of trough blood CsA levels.

Hypertension can occur in the presence of normal renal function, indicating that the hypertensive etiology is probably not via renal failure. One possible cause of CsA-induced hypertension may be increased renal vascular resistance mediated via an imbalance of local eicosanoid production [6]. The hypertension is dose dependent and reversible, in the early stages, by dose reduction; otherwise treatment should involve sodium restriction and/or the use of diuretics or calcium channel blockers.

The risk of malignancy with the low doses of CsA used in skin disease is uncertain, but is likely to be very low. To date, no definite cases of malignancy with a direct causal relationship to CsA have been reported. Other side-effects are commoner but are mild, reversible, and include gingival hyperplasia, tremor, hypertrichosis, headaches, diarrhea, malaise, and nausea.

In view of these limiting, dose-dependent, side-effects of CsA, an intensive search for an effective topical preparation of the drug for psoriasis is underway, but at present none has been found despite the use of a number of different vehicles. This lack of response raises the question of whether this is due to non-penetration of the epidermis by topically applied CsA or CsA not working locally in psoriasis and needing to be administered systemically. This has been addressed by the use of intralesional CsA. In two studies [7,8] significant improvement or clearance of treated plaques was achieved using three injections/week of a 17 mg/ml CsA solution for 4 weeks. This response occurred in the absence of significant blood levels of CsA, thereby suggesting that the failure of topical CsA preparations is perhaps one of non-absorption resulting from binding of CsA to stratum corneum lipids, rapid partitioning of CsA into subcutaneous tissues, or cytochrome p450-mediated metabolism in the skin. Unfortunately, intralesional CsA is not a viable treatment option for psoriasis because of the unacceptable pain experienced at the injection site.

MECHANISM OF ACTION

Attention has always focused on the striking and unique immunosuppressive properties of CsA, which were first elucidated by Borel in 1976 [1], and indeed much subsequent work and therapeutic intervention has laid great emphasis on this effect. However, from the outset of CsA research it was known that this drug had effects on other cell types and was not T-cell specific. The principal effect of CsA is in suppressing a T-cell mediated response with a predilection for the $CD4^+$ T-cell subset. CsA intervenes early in T-cell activation by inhibiting the transcription of T-cell–derived lymphokines mRNA such as gamma interferon, macrophage chemotactic factor, and macrophage inhibitory factor. T-cell production of interleukin-2 is also blocked by CsA inhibition of mRNA transcription of this lymphokine, thereby inhibiting further activation and recruitment of T cells [3].

The cytoplasmic receptor for CsA is the ubiquitous protein, cyclophilin, now known to be identical to peptidyl-prolyl cis-trans isomerase, a necessary enzyme in the process of protein folding. It has been demonstrated that binding of CsA to this molecule inhibits the subsequent folding of proteins. This could result in the inhibition of lymphocyte activation and lymphokine gene transcription [9].

As stated previously, the first reports of the efficacy of CsA in psoriasis were purely anecdotal; however, in 1986, Valdimarsson put forward a hypothesis [10] that psoriasis was a T-cell–mediated disease and should by definition respond to CsA. This has been shown to be an accurate prediction, and, for the most part, subsequent studies of the mechanism of action of CsA in psoriasis have strongly implicated an inhibition of T-cell function. Baker et al [11] and Gupta et al [12] have demonstrated by immunohistochemical staining of skin biopsies taken from psoriatic plaques during oral CsA therapy that the earliest immune cell changes observed during resolution of psoriasis are a reduction in $HLA\text{-}DR^+$ $CD1^-$ dendritic cells in the epidermis coupled with a decrease in epidermal and dermal $CD4^+$ and $CD8^+$ T cells. As the epidermal $HLA\text{-}DR^+CD1^-$ dendritic cells decrease prior to any clinical improvement [8,11] this observation implies an important role for these cells in the maintenance of psoriatic plaques. As to whether these cells are immature Langerhans cells [11] or a heterogeneous $HLA\text{-}DR^+$ antigen-presenting cell population [12] remains to be clarified. The loss of class II HLA-DR expression by these cells may be a manifestation of CsA-induced reduction of gamma interferon production by activated T cells, thus decreasing interactions between T cells and $HLA\text{-}DR^+$ antigen-presenting and accessory cells.

Cooper [4] has also shown that CsA reduces the functional capability of antigen-presenting cells in both involved and uninvolved epidermis as well as reducing the numbers present in a psoriatic plaque. Further evidence for a direct inhibition of T-cell function as a mechanism of action of CsA comes from a study by Ho et al [3] in which intralesional CsA was used to treat chronic plaque psoriasis. In this study the first immunologic change observed in the treated plaques at 5 d, before either a reduction in epidermal T-cell numbers or clinical improvement occurred, was a decrease in epidermal keratinocyte ICAM-1 expression. This observation can be interpreted as an inhibition of T-cell lymphokine production, as T-cell–derived gamma-interferon is required for induction of keratinocyte ICAM-1 expression. ICAM-1 expression by the keratinocyte is responsible for allowing lymphocytes to bind to keratinocytes via LFA-1/ICAM-1 interactions and is an important participant in intraepidermal lymphocyte trafficking (see Nickoloff and Griffiths, this issue, p 35S) as it pertains to the pathogenesis of inflammatory dermatoses, including psoriasis.

Although there is strong evidence for an immunologic mechanism of action for CsA in psoriasis, there is also support for an effect on other cell types, most importantly the keratinocyte. In vitro studies have demonstrated that CsA has a direct anti-proliferative effect on human keratinocytes, as well as fibroblasts grown in serum-free but not those grown in serum-containing, media [13,15], and on murine keratinocytes grown in serum-containing media [14].

Phorbol ester-treated mouse skin has been used as a model for the inflammatory hyperplastic aspects of psoriasis [15]. In this model, although CsA inhibits the protean responses of mouse skin to phorbol ester, the site of action appears to be distal to protein kinase C-mediated transduction events. This same study provided further evidence for a direct effect of CsA on keratinocyte function in that the induction of membrane-associated, protein kinase-C-dependent transglutaminase activity (found primarily in keratinocytes) was inhibited by CsA. Elder, at this meeting, has demonstrated that psoriatic epidermis contains increased levels of TGF-alpha, mRNA. The findings of Nickoloff and Griffiths (also presented at this meeting) that CsA will inhibit EGF-receptor expression in cultured keratinocytes introduces another CsA-sensitive event whereby TGF-alpha (which shares the EGF-receptor) cannot exert its putative in-vivo hyperproliferative effect on psoriatic keratinocytes.

In summary, the mode of action of CsA in psoriasis seems to be predominantly one of inhibition of $CD4^+$ T lymphocyte function, but evidence is mounting that there may be other effects on other cell types, most notably antigen-presenting cells and the keratinocyte. The precise molecular mechanisms are still poorly elucidated, but if and when they are, this knowledge can be used to profit the clinician. The advent of CsA has provided us with a new and remarkably effective treatment for severe psoriasis, although it is hindered by dose-dependent side-effects. The current European and

North American multi-center, dose-finding studies, coupled with long-term evaluations and the search for an effective topical preparation will provide clearer guidelines for the future use of CsA in this disease.

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